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Regulation of T-cell–mediated pathology: The revival of suppressor cells

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Diseases resulting from an overactive (autoimmunity) or underactive (chronic parasitic infections) immune response have long been subjects of investigation. The phenomenon of active immunosuppression was observed decades ago, but not until the recent advances in cellular immunology was credibility established. Within the past 10 years, a subset of $CD4^+$ T cells expressing the alpha chain of the interleukin (IL)-2 receptor (CD25) has been identified in mice and humans as potent suppressors of T-cell responses. In addition to naturally occurring $CD4^+$ $CD25^+$ T cells, many T cells can be induced to acquire regulatory functions.

Although first identified as suppressors of autoimmunity, $CD4^+$ $CD25^+$ T cells have been shown to control immune responses to autoantigens, alloantigens, tumor antigens, and foreign pathogenic antigens. It is now theorized that their presence is not to control self-reactive T cells, but rather to maintain an appropriate response against all antigens. In vitro analysis indicates that $CD4^+$ $CD25^+$ T cells act in a cell-contact-dependent manner resulting in the inhibition of IL-2 production in responding T cells. Recent reports show the localization of $CD4^+$ $CD25^+$ T cells in the draining lymph node and tissues involved in the immune response. These cells are seen in contact with both responding T cells and antigen-presenting cells (APC). Although, much in vivo data indicate that production of IL-10 is required for suppressive function, this work demonstrates that cell contact may also be a mechanism for $CD4^+$ $CD25^+$ T-cell–mediated suppression in vivo.

It was recently demonstrated that antibody signalling through the glucocorticoid-induced tumor necrosis factor receptor (TNFR) (GITR) regulates suppressor cell function. The ligand for GITR (GITR-L) has also been shown to overcome suppression by $CD4^+$ $CD25^+$ T cells. GITR-L is expressed on a broad range of APC. Perhaps regulated expression of GITR-L controls the ability of responding cells to mount an appropriate immune response. Therapeutically targeting GITR/GITR-L interactions may allow for manipulation of $CD4^+$ $CD25^+$ T-cell–mediated suppression. Engagement of GITR would decrease suppressive function for induction of tumor immunity or enhancing vaccines. Conversely, blocking GITR-L could enhance their suppression for amelioration of autoimmunity or graft rejection.

Although much cellular and molecular characterization has been performed on these cells, there are still many unanswered questions. At the forefront are the following: How do $CD4^+$ $CD25^+$ T cells deliver the suppressive signal? What is the interaction of $CD4^+$ $CD25^+$ T cells with other regulatory T-cell populations or regulatory dendritic cells? Perhaps most important, will these "suppressor" cells stand the test of time?

ADDITIONAL READING

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